

WHAT IS CLAIMED IS:

1 1. A method for modulating expression of a mammalian SREBP-1 gene,
2 the method comprising administering a modulator compound that promotes or inhibits
3 LXR α -mediated expression of the SREBP-1 gene to a cell that comprises an SREBP-1 gene
4 and an LXR α polypeptide.

1 2. The method of claim 1, wherein the modulator compound is an agonist
2 of LXR α and promotes LXR α -mediated expression of the SREBP-1 gene.

1 3. The method of claim 1, wherein the modulator compound promotes or
2 inhibits LXR α -mediated expression of the SREBP-1c transcript.

1 4. The method of claim 2, wherein the modulator compound is 24,25-
2 epoxycholesterol.

1 5. The method of claim 1, wherein the modulator compound is an
2 antagonist of LXR α and inhibits LXR α -mediated expression of the SREBP-1 gene.

1 6. The method of claim 5, wherein the cell further comprises one or more
2 genes that encode an enzyme involved in fatty acid and triglyceride metabolism and
3 contacting the cell with the modulator compound inhibits expression of one or more of the
4 genes that encode an enzyme involved in fatty acid and triglyceride metabolism.

1 7. The method of claim 1, wherein the enzyme involved in fatty acid and
2 triglyceride metabolism is selected from the group consisting of fatty acid synthase, acetyl
3 CoA carboxylase, steroyl CoA desaturase, and lipoprotein lipase.

1 8. The method of claim 1, wherein the cell is in a mammal.

1 9. The method of claim 8, wherein the mammal is a human.

1 10. The method of claim 8, wherein the modulator compound is an
2 antagonist of LXR α and triglyceride levels in the mammal are reduced.

1 11. The method of claim 8, wherein the modulator compound is an
2 antagonist of LXR α and insulin levels in the mammal are reduced.

1 12. A method of modulating triglyceride levels in a mammal, the method
2 comprising administering to the mammal an effective amount of a modulator compound that
3 inhibits LXR α -mediated expression of an SREBP-1 gene in cells of the mammal.

1 13. The method of claim 12, wherein mammal is a human.

1 14. A method of prescreening to identify a candidate therapeutic agent that
2 modulates SREBP-1 expression in a mammal, the method comprising:

3 providing a reaction mixture which comprises:

4 a polypeptide that comprises an LXR α ligand binding domain

5 (LBD);

6 a ligand for LXR α ; and

7 a test compound; and

8 determining whether the amount of LXR α ligand that binds to the LBD
9 is increased or decreased in the presence of the test compound relative to the amount of
10 ligand that binds to the LBD in the absence of the test compound;

11 wherein a test compound that causes an increase or decrease in the
12 amount of LXR α ligand binding to the LBD is a candidate therapeutic agent for modulation
13 of SREBP-1 expression in a mammal.

1 15. The method of claim 15, wherein the method further comprises
2 administering the candidate therapeutic agent to a cell which comprises a SREBP-1 gene to
3 determine whether the candidate therapeutic agent modulates expression of the SREBP-1
4 gene in the cell, and/or expression of a gene that is regulated by SREBP-1.

1 16. The method of claim 15, wherein the gene that is regulated by SREBP-
2 1 encodes an enzyme involved in fatty acid and/or triglyceride metabolism.

1 17. The method of claim 16, wherein the enzyme involved in fatty acid
2 and/or triglyceride metabolism is selected from the group consisting of fatty acid synthase,
3 acetyl CoA carboxylase, steroyl CoA desaturase, and lipoprotein lipase.

1 18. The method of claim 15, wherein the gene that is regulated by SREBP-
2 1 encodes an enzyme involved in adipocyte differentiation.

- 1 19. The method of claim 15, wherein the cell is in a mammal.
- 1 20. The method of claim 14, wherein the ligand for LXR α is a peptide
2 sensor.
- 1 21. The method of claim 20, wherein the peptide sensor is derived from an
2 RXR.
- 1 22. The method of claim 20, wherein the peptide sensor is derived from a
2 coactivator or corepressor.
- 1 23. The method of claim 22, wherein the coactivator is SRC-1 or NCOR.
- 1 24. The method of claim 20, wherein the peptide sensor is derived from a
2 coactivator and comprises an amino acid sequence LXXLL, where X is any amino acid.
- 1 25. The method of claim 20, wherein the peptide sensor is derived from a
2 corepressor and comprises an amino acid sequence IXXII, where X is any amino acid.
- 1 26. The method of claim 20, wherein the peptide sensor comprises a
2 detectable label.
- 1 27. The method of claim 14, wherein the ligand for LXR α is a coactivator
2 or corepressor.
- 1 28. The method of claim 14, wherein the ligand for LXR α is an oxysterol.
- 1 29. The method of claim 28, wherein the oxysterol is 24,25-
2 epoxycholesterol.
- 1 30. The method of claim 14, wherein the amount of binding is determined
2 using a FRET assay.
- 1 31. The method of claim 14, wherein the amount of binding is determined
2 using a fluorescence polarization assay.
- 1 32. The method of claim 14, wherein the amount of binding is determined
2 using ELISA.

1 33. The method of claim 14, wherein the amount of binding is determined
2 using a direct binding assay.

1 34. A method for ameliorating a condition associated with abnormal
2 SREBP-1 expression in a mammal, the method comprising administering to the mammal a
3 therapeutically effective amount of a LXR α antagonist.

1 35. The method of claim 34, wherein the condition associated with
2 abnormal SREBP-1 expression is hypertriglyceridemia.

1 36. The method of claim 34, wherein the condition associated with
2 abnormal SREBP-1 expression is lipodystrophy.

1 37. The method of claim 36, wherein the lipodystrophy is congenital
2 generalized lipodystrophy.

1 38. The method of claim 34, wherein the condition associated with
2 abnormal SREBP-1 expression is insulin resistance.

1 39. The method of claim 34, wherein the condition associated with
2 abnormal SREBP-1 expression is an elevated plasma insulin level.

1 40. The method of claim 34, wherein the condition associated with
2 abnormal SREBP-1 expression is hyperglycemia and/or diabetes mellitus.

1 41. The method of claim 34, wherein the condition associated with
2 abnormal SREBP-1 expression is a syndrome associated with treatment of AIDS by
3 administration of an HIV protease inhibitor, which syndrome is characterized by one or more
4 of lipodystrophy, insulin resistance and hyperlipidemia.